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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Jan Brundell and Lena Nyberg
Application No.	:	09/202,463
Filed	:	August 19, 1999
For	:	METHODS FOR DETERMINING THE PRESENCE OF BRAIN PROTEIN S-100

Examiner	:	Sharon L. Turner
Art Unit	:	1647
Docket No.	:	260044.401
Date	:	May 28, 2003

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ANNE-CHARLOTTE ARONSSON
UNDER 37 C.F.R. § 1.132

Dear Commissioner:

Considered
6-15-03

I, Anne-Charlotte Aronsson, declare that:

1. I, Anne-Charlotte Aronsson, am PhD in biochemistry and International Marketing Manager at DiaSorin AB.

2. I have reviewed the Office Action dated December 31, 2002, in the subject application, including the rejection under 35 U.S.C. § 103 and the cited art, and submit this Declaration for the purpose of providing evidence to the Examiner that the

cited references, including Van Eldik *et al.*, Okada *et al.*, and Shibue *et al.*, alone or in combination, do not render obvious the invention of the subject application.

3. I submit that the claimed invention is directed to methods and kits comprising two distinct monoclonal antibodies, each specific for a different region of S100β. After carefully reviewing Van Eldik *et al.*, I submit that an ordinarily skilled artisan would not believe that this reference describes two distinct monoclonal antibodies specific for S100β, for reasons described in detail below. Furthermore, I submit that the results published in Van Eldik *et al.*, in light of the general knowledge in the art, strongly suggest that the number of epitopes of S100β may be very limited and that only a single S100β-specific epitope may exist. Accordingly, the artisan of ordinary skill would not have found it obvious, in light of Van Eldik *et al.*, Okada *et al.*, and Shibue *et al.* to develop an ELISA assay that requires two antibodies specific for different epitopes of S100β.

4. Van Eldik *et al.* describes the identification of two hybridoma lines that produce monoclonal antibodies specific for S100β. However, the characterization and analysis of the two hybridoma lines presented in Van Eldik *et al.* strongly suggests that they produce the same antibody. As stated on page 6035, column 2, paragraph 5, "[b]oth monoclonal antibodies are of the IgG1k isotype. In all characterizations done to date, the two monoclonal antibodies are indistinguishable in their reactivities" (emphasis added). Indeed, Van Eldik *et al.* provides no evidence that the two antibodies are in any way different. Furthermore, it appears that the authors, themselves, believed that the two hybridomas produced the same antibody, since all of the subsequent experiments described in Van Eldik *et al.* were performed using a single antibody. Based on this evidence, I submit that one of ordinary skill in the art would believe that the two hybridoma lines identified in Van Eldik *et al.* almost certainly produce antibodies against the same epitope of S100β, thereby excluding the possibility that they could be used according to the invention in a dual-antibody assay for S100β.

5. I also submit that the fact that Van Eldik *et al.* were unable to produce more than one antibody specific for S100β would discourage one from even

attempting to develop a dual-antibody assay for S100β, since such an assay requires two antibodies specific for different epitopes of S100β. The skilled artisan would recognize that the number of S100β specific epitopes present in the S100β polypeptide is probably very small, given the small size of the S100β polypeptide and its substantial homology to other S100 polypeptides. Indeed, the teachings of Van Eldik *et al.* points to the fact that the number of epitopes on S100β may be very limited and that only a single S100β specific epitope may be present in the entire polypeptide. Thus, the skilled artisan, based upon the teachings of Van Eldik *et al.*, would have no reasonable expectation of being able to successfully produce two distinct monoclonal antibodies against S100β, as required to perform the claimed method or produce the claimed kit. Furthermore, even if an additional epitope existed, it appears likely, based upon the small size of the S100β protein and its significant homology to other S100 family members over extensive regions, that epitopes specific for S100β would sterically hinder each other, and, therefore, would not be useful in the practice of the claimed invention. Therefore, I submit that the claimed invention would not have been obvious in view of the combined references.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

2003-05-16
Date

Dr Anne-Charlotte Aronsson

WTC:jto

Enclosures:
Postcard

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
(206) 622-4900
Fax: (206) 682-6031